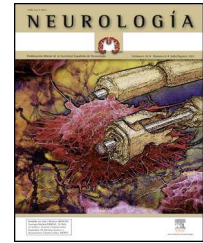




# NEUROLOGÍA

[www.elsevier.es/neurologia](http://www.elsevier.es/neurologia)



## CONSENSUS STATEMENT

## Drug-resistant epilepsy: Definition and treatment alternatives<sup>☆</sup>



F.J. López González<sup>a,\*</sup>, X. Rodríguez Osorio<sup>a</sup>, A. Gil-Nagel Rein<sup>b</sup>,  
M. Carreño Martínez<sup>c</sup>, J. Serratosa Fernández<sup>d</sup>, V. Villanueva Haba<sup>e</sup>,  
A.J. Donaire Pedraza<sup>c</sup>, J.M. Mercadé Cerdá<sup>f</sup>

<sup>a</sup> Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, La Coruña, Spain

<sup>b</sup> Hospital Rúber Internacional, Madrid, Spain

<sup>c</sup> Hospital Clínic, Barcelona, Spain

<sup>d</sup> Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

<sup>e</sup> Hospital Universitario La Fe, Valencia, Spain

<sup>f</sup> Hospital Regional Universitario Carlos Haya, Málaga, Spain

Received 18 March 2014; accepted 23 April 2014

Available online 11 August 2015

### KEYWORDS

Drug-resistant epilepsy;  
Rational combination therapy;  
Epilepsy surgery;  
Deep brain stimulation;  
Vagus nerve stimulation;  
Ketogenic diet

### Abstract

**Introduction:** Drug-resistant epilepsy affects 25% of all epileptic patients, and quality of life decreases in these patients due to their seizures. Early detection is crucial in order to establish potential treatment alternatives and determine if the patient is a surgical candidate.

**Development:** PubMed search for articles, recommendations published by major medical societies, and clinical practice guidelines for drug-resistant epilepsy and its medical and surgical treatment options. Evidence and recommendations are classified according to the criteria of the Oxford Centre for Evidence-Based Medicine (2001) and the European Federation of Neurological Societies (2004) for therapeutic actions.

**Conclusions:** Identifying patients with drug-resistant epilepsy is important for optimising drug therapy. Experts recommend rational polytherapy with antiepileptic drugs to find more effective combinations with fewer adverse effects. When adequate seizure control is not achieved, a presurgical evaluation in an epilepsy referral centre is recommended. These evaluations explore how to resect the epileptogenic zone without causing functional deficits in cases in which this is feasible. If resective surgery is not achievable, palliative surgery or neurostimulation systems (including vagus nerve, trigeminal nerve, or deep brain stimulation) may be an option. Other treatment alternatives such as ketogenic diet may also be considered in selected patients.

© 2014 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. All rights reserved.

<sup>☆</sup> Please cite this article as: López González FJ, Rodríguez Osorio X, Gil-Nagel Rein A, Carreño Martínez M, Serratosa Fernández J, Villanueva Haba V, et al. Epilepsia resistente a fármacos. Concepto y alternativas terapéuticas. Neurología. 2015;30:439–446.

\* Corresponding author.

E-mail address: [javieritol@yahoo.com](mailto:javieritol@yahoo.com) (F.J. López González).

**PALABRAS CLAVE**

Epilepsia refractaria;  
 Politerapia racional;  
 Cirugía epilepsia;  
 Estimulación cerebral profunda;  
 Estimulación vagal;  
 Dieta cetógena

**Epilepsia resistente a fármacos. Concepto y alternativas terapéuticas****Resumen**

**Introducción:** La epilepsia resistente al tratamiento médico afecta a una cuarta parte de los pacientes con epilepsia. Como consecuencia de las crisis estos pacientes presentan una peor calidad de vida, por lo que es fundamental su diagnóstico para establecer posibles alternativas terapéuticas e iniciar una valoración prequirúrgica.

**Desarrollo:** Búsqueda de artículos en PubMed y recomendaciones de las Guías de Práctica Clínica (GPC) y Sociedades Científicas más relevantes, referentes a epilepsia refractaria y al tratamiento médico y quirúrgico. Se clasifican las evidencias y recomendaciones según los criterios pronósticos del *Oxford Centre for Evidence Based Medicine* (2001) y de la *European Federation of Neurological Societies* (2004) para actuaciones terapéuticas.

**Conclusiones:** La identificación de los pacientes con epilepsia refractaria es importante para optimizar el tratamiento farmacológico. Se recomienda el empleo de una politerapia racional de fármacos antiepilépticos, buscando combinaciones que aumenten la eficacia y minimicen los efectos adversos. Cuando no se consigue el control adecuado de las crisis es necesario realizar una valoración prequirúrgica en un centro especializado, con el fin de reseca la zona epileptógena sin producir déficits al paciente en los casos en los que sea posible. En caso contrario se recurrirá a procedimientos de cirugía paliativa o sistemas de neuroestimulación (vagal, trigeminal o cerebral). Otras alternativas, como la dieta cetógena, también pueden considerarse en pacientes seleccionados.

© 2014 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

**Introduction**

Identifying patients with drug-resistant epilepsy is essential in order to optimise drug treatment, start the evaluation process to determine if they are candidates for surgery, and opt for surgery or other non-pharmacological alternatives on a case-by-case basis.

The methodological steps followed in drafting this chapter of the Official Clinical Practice Guidelines for Epilepsy were described in the first chapter of the guidelines, published as an article in *Neurología*. Classification of the levels of evidence and the grades of recommendation is in accordance with the 2004 European Federation of Neurological Societies guidelines regarding therapeutic actions, and the modified version of the Oxford Centre for Evidence-Based Medicine levels of evidence (2001) for prognostic studies.

**Drug-resistant epilepsy**

The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.<sup>1</sup> Seizure freedom is considered to be sustained when the patient is seizure-free for more than one year, or has sporadic seizures separated by a period three times the longest interval between seizures prior to the treatment, whichever is longer. About 25% of all patients with epilepsy present drug-resistant epilepsy.<sup>2</sup> As a consequence of poor control over their epileptic seizures (ES), they present an increased risk of early death, trauma,

and psychosocial alterations, while their quality of life is diminished. Drug-resistant epilepsy may show temporary remission periods (4% of adult cases yearly, with higher rates in children) but ES frequently reappear. Therefore, identifying patients with drug-resistant epilepsy is essential in order to start preparing the presurgical evaluation, and to arrange for possible therapeutic alternatives in specialised units or centres.

**Prognostic factors for developing drug-resistant epilepsy**

The risk factors associated with a poor prognosis for epilepsy are age-dependent.

- In children (prospective study)<sup>3</sup>: age younger than one year, symptomatic epilepsy, mental retardation or overall developmental delay, pathological neuroimaging study, or a high seizure frequency prior to being diagnosed with drug-resistant epilepsy (level of evidence [LE] II).
- In children (prospective study)<sup>4</sup>: weekly seizures during the first year of treatment, weekly seizures prior to treatment onset, or remote symptomatic epilepsy (LE I).
- In adolescents<sup>5</sup>: focal epilepsy, mental retardation or psychiatric disturbances (LE II).
- In adults (prospective study)<sup>6</sup>: symptomatic focal epilepsy, initial consciousness impairment during seizures, multiple seizure types, tonic-akinetic seizures, or anomalies on the electroencephalogram (EEG) (LE IV).

**Table 1** Antiepileptic drugs that can increase seizure frequency or exacerbate seizures in certain types of epilepsy.

Type of seizure/syndrome	CBZ	OXC	PHT	PGB	LTG	VPA	GBP	VGB	TGB	BZDs
Absence seizures	↑↑↑	↑	↑↑↑			↑	↑	↑↑	↑	
Myoclonias	↑↑↑	↑	↑↑↑	↑↑↑	↑		↑	↑	↑	
Juvenile myoclonic epilepsy	↑↑	↑	↑↑		↑					
Lennox–Gastaut synd.	↑↑	↑	↑↑		↑		↑	↑↑		↑↑
Rolandic epilepsy	↑↑				↑	↑				
Dravet synd.	↑				↑↑			↑		
Landau–Kleffner synd.	↑		↑							
Continuous spike-wave during sleep	↑		↑							

BZD, benzodiazepines; CBZ, carbamazepine; GBP, gabapentin; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; TGB, tiagabine; VGB, vigabatrin; VPA, valproic acid.

There is not enough information for the latest AEDs: lacosamide (LCM), eslicarbazepine (ESL), retigabine (RTG), perampanel (PER).

Potential for exacerbation: ↑limited; ↑↑moderate; ↑↑↑ significant.

### Causes of diagnostic errors in drug-resistant epilepsy

Evaluation of patients with drug-resistant epilepsy in a specialised centre permits exclusion of cases of pseudo-resistance (up to 25% of the patients referred to a specialised centre do not have epilepsy, and their most frequent final diagnoses are syncope, non-epileptic seizures, and sleep disorders).<sup>7</sup> Video-EEG monitoring is essential for identifying seizure characteristics. Medical treatment should be optimised since some AEDs are effective against certain types

of ES but exacerbate others (Table 1). The patient should receive advice on factors that can make control of ES difficult, such as treatment non-compliance, sleep deprivation, intercurrent diseases, alcohol use, hormonal changes, or drug interactions.<sup>8,9</sup>

### Drug treatment optimisation

Rational polytherapy is recommended in patients with drug-resistant epilepsy, with the aim of finding AED combinations

**Table 2** Associated antiepileptic drugs (AED).

	Type of epilepsy
<i>Associated AEDs that may be useful</i>	
VPA + ESM	Childhood absence epilepsy
VPA + LTG	Epilepsy with absence seizures
	Juvenile myoclonic epilepsy
	Focal epilepsy
LCM + AEDs other than sodium-channel blockers	Focal epilepsy
CBZ/OXC/ESL + VPA	Focal epilepsy
	Second. gen. focal epilepsy
CBZ/OXC/PHT/ESL + GBP/LEV/PGB/LCM/ZNS	Focal epilepsy
LTG/VPA + GBP/LEV/PGB/TPM/ZNS/LCM	Focal epilepsy
	Lennox–Gastaut syndrome
CBZ/PHT + TGB/TPM	Focal epilepsy
<i>AED associations that should be monitored</i>	
PB/PRM + CBZ/PHT/VPA	Focal epilepsy
	Second. gen. focal epilepsy
CBZ/OXC/PHT + LTG	Focal epilepsy
PHT + VPA	Focal epilepsy
CBZ/PHT + TGB/TPM	Focal epilepsy
<i>Not recommended AED associations</i>	
PB/PRM + CZP/CLB	Focal epilepsy
	Second. gen. focal epilepsy
PB/PRM + LTG/TGB/TPM	Focal epilepsy
CBZ + PHT	Focal epilepsy
	Second. gen. focal epilepsy
OXC + ESL	Second. gen. focal epilepsy

CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; PB, phenobarbital; PRM, primidone; TPM, topiramate; ZNS, zonisamide.

Recommendations for drug-resistant epilepsy (DRE)	Grade of recommendation
Diagnostic error or inappropriate treatment should be ruled out for every patient with suspected DRE.	C
Patients with suspected DRE should be referred to a medical/ surgical unit specialising in epilepsy for a full evaluation.	Ge-sen
Video-EEG monitoring is an essential procedure that will usually show a clear difference paroxysmal events. This procedure should be applied to every patient with suspected DRE.	C
Doctors should propose different untried but indicated AEDs to every patient with DRE who lacks non-pharmacological alternatives.	C
When associating an AED with other drugs, seizure and syndrome type, existing AEDs, and patient characteristics must all be considered (TABLE II).	C

**Figure 1** Recommendations for drug-resistant epilepsy.

that increase efficacy (supra-additive effect) and minimise adverse effects (infra-additive effect)<sup>10</sup> (Table 2):

- Combining AEDs with different action mechanisms to achieve a broad action spectrum intended to cover all types of ES experienced by the patient.<sup>11–15</sup>
- Avoiding AEDs with similar toxicity profiles and adjusting doses according to the patient's characteristics (age, sex, physical condition, and comorbidities).
- Considering that using more than 2 AEDs tends to result in more numerous adverse effects rather than a real improvement in seizure control (especially in elderly or polymedicated patients).
- Customising treatment for type of ES, type of epilepsy, and even epileptic syndrome by aetiology or gene (avoiding AEDs that block sodium channels in patients with mutations in the sodium channel gene *SCN1A* that causes Dravet syndrome).

### Number of antiepileptic drugs to try in cases of drug-resistance epilepsy not treatable by surgery

Most authors recommend trying all novel AEDs until achieving control over drug-resistant epilepsy, provided that those drugs are indicated for the patient's ES or epilepsy type.<sup>16</sup> A systematic review and meta-analysis of the efficacy of all novel AEDs as adjunctive treatment for drug-resistant epilepsy found total control over ES in about 6% of all patients and a reduction in critical frequency in 21%<sup>17</sup> (LE I). Population studies in patients with drug-resistant epilepsy

describe long remission periods thanks to successive changes in medication (8%-28%)<sup>18,19</sup> (LE III).

Fig. 1 presents the consensus recommendations issued by the authors of the Official Clinical Practice Guidelines for drug-resistant epilepsy.

### Epilepsy surgery

Epilepsy surgery is aimed at eliminating or reducing ES by excising the epileptogenic zone without causing deficits in the patient (resection surgery). Approximately 5% of all patients may benefit from surgical epilepsy treatment.<sup>20</sup> If epilepsy surgery is not possible, disconnective procedures or vagal nerve or brain stimulation will be used.<sup>21,22</sup>

Indications for surgery include:

1. Patients with drug-resistant epilepsy and seizures that interfere with their daily lives. In children, special attention must be paid to the adverse effects of AEDs.<sup>23</sup>
2. The progression timeline of epilepsy should have reached at least 2 years, except in patients with life-threatening seizures or in children.
3. Epilepsies that can be treated with surgery: surgically remediable epileptic syndrome (poor control with drugs and good results with surgery), or when surgery can improve epilepsy with acceptable sequelae, in light of the baseline situation and seizure severity.<sup>24</sup>

Absolute or relative contraindications are listed below.

- Age does not represent an absolute contraindication; the risk/benefit ratio in elderly patients should be assessed.
- Cause of epilepsy: surgery is not considered when the aetiology is a progressive neurological disease, with the exception of Rasmussen encephalitis.
- Concomitant diseases contraindicate surgery if they have significant effects on vital or functional prognosis.
- Concomitant psychiatric disorders contraindicate surgery if they may compromise the surgical result or subsequent follow-up.
- IQ score below 70 indicates a poorer prognosis, but it is not a contraindication.

### Selection of candidates for surgery

Epilepsy surgery currently requires a multidisciplinary team of specialists with specific training, working together in the same unit and equipped with the necessary technological means.<sup>25</sup> This team should include epileptologists, neurologists and/or paediatric neurologists, neurosurgeons, structural and functional neuroimaging specialists, neuropsychologists, psychiatrists, nursing staff specifically trained in epilepsy, and EEG technicians. Presurgical evaluation of patients will consist of examinations aimed at identifying the location and extension of the epileptogenic zone, and assessing the potential impact of surgery on the patient's neurological and cognitive functions and the emotional status.<sup>26</sup> In addition to clinical assessment, doctors initially order a series of complementary studies: video-EEG, brain MRI with epilepsy protocol, neuropsychological studies, and a psychiatric evaluation. Certain cases will require more specific studies, such as functional MR imaging, Wada test, ictal SPECT, SISCOM images, PET images, magnetoencephalography, electrocorticography, or semi-invasive or invasive electrodes.<sup>27</sup> We recommend that the final decision on surgical treatment be made in a meeting of all members of the multidisciplinary team.

### Surgically treatable epilepsy

#### Epilepsy treatable with surgical resection procedures

- *Mesial temporal lobe epilepsy secondary to hippocampal sclerosis.* Amygdalohippocampectomy is usually performed along with anterior temporal lobectomy, after which two-thirds of patients normally become seizure free. Surgery and subsequent treatment with AEDs provide better seizure control than medical treatment alone<sup>28,29</sup> (LE I). A randomised clinical trial has observed that total hippocampectomy might be associated with a better response regarding ES control, with no increase in associated neuropsychological morbidity<sup>30</sup> (LE II). The decision to spare or resect the superior temporal gyrus does not impact surgery outcomes or performance of confrontation naming tasks<sup>31</sup> (LE II). Patients with hippocampal sclerosis are generally referred late for surgical assessment, even though early surgery is more effective than AED treatment<sup>32,33</sup> (LE II).
- *Neocortical epilepsies with a single circumscribed lesion.* Lesionectomy is the indicated procedure. The epileptogenic zone is located in the immediate vicinity of the structural lesion and MRI scans are usually sufficient

**Table 3** Results of epilepsy surgery. Seizure-free patients.

Procedure	ES-free patients
<b>Surgically treatable syndromes</b>	
<i>Mesial temporal epilepsy (amygdalohippocampectomy without/with anterior temporal lobectomy)</i>	70%-80%
<i>Neocortical epilepsies with single circumscribed lesion (lesionectomies):</i>	
Temporal	70%-80%
Extratemporal	60%-70%
<b>Other surgically treatable syndromes with poorer outcomes</b>	
<i>Neocortical epilepsies with single badly-circumscribed lesion:</i>	
Temporal	66%
Frontal	27%-34%
Parietal	46%
Occipital	46%
<i>Non-lesional epilepsy:</i>	
Temporal	60%
Extratemporal	35%

to guide surgery. Invasive studies may be necessary to define the limits of the epileptogenic zone. Rates of seizure freedom in series of patients after temporal lobe surgery are similar to those observed in patients treated with temporomesial resection associated with hippocampal sclerosis and slightly higher than results following extratemporal surgery.<sup>34</sup> The ILAE recently issued new recommendations for surgery in cases of ES secondary to cavernomas.<sup>35</sup>

- *Hemispheric syndromes.* Principal types include hemimegalencephaly, Sturge–Weber syndrome, Rasmussen syndrome, and other unilateral catastrophic epilepsies. These syndromes are treated surgically with hemispherectomy or functional hemispherectomy. Some 60% to 80% of patients remain seizure-free after surgery<sup>36</sup> (LE III). Candidates are patients with prior hemiparesis and loss of useful function in the hand contralateral to the affected hemisphere.
- *Other surgically treatable syndromes with poorer outcomes: neocortical epilepsies with no single circumscribed lesion.* Surgery involves resecting the neocortical area identified as the zone where the ES begin. It is used in patients with dual pathology, poorly circumscribed lesions and even patients without visible lesions on neuroimaging studies. In epilepsy without lesions, surgery uses the results of functional studies (EEG, SPECT, and PET) as a guide for placing intracranial electrodes. In cases of temporal epilepsy, as many as 60% of all patients attain seizure freedom, but this rate decreases to 35% for extratemporal locations<sup>37–39</sup> (LE IV).

Table 3 displays prognostic data for the different surgical procedures.



Recommendations for epilepsy surgery	Grade of recommendation
In drug-resistant temporal lobe epilepsy, epilepsy surgery has proven more effective than pharmaceutical treatment for achieving seizure freedom and better quality of life.	A
Complete hippocampal resection is associated with better outcomes than partial resection for controlling ES. Furthermore, poorer neuropsychological performance is not observed after surgery.	B
Epilepsy surgery is indicated for candidates with seizure location other than the temporal lobe.	Ge-sen
Functional hemispherectomy or its variants are indicated in unilateral hemispheric convulsive syndromes, which are resistant to AEDs.	C
Vagal nerve stimulation is an effective therapeutic alternative in children and adults with DRE who are not candidates for resection surgery.	A
Bilateral stimulation of the anterior nuclei of the thalamus could be a therapeutic alternative for patients with DRE who are not candidates for resection surgery.	B

**Figure 2** Recommendations for epilepsy surgery.

### Palliative surgery

Palliative surgery includes procedures aimed at reducing ES so as to improve patients' quality of life.

- *Multiple subpial resection.* Today this procedure is used exclusively in eloquent areas in such disorders as Landau–Kleffner syndrome. Up to 55% of patients are seizure-free, and 4% display permanent deficits.<sup>26</sup>
- *Corpus callosotomy.* Partial or total sectioning of the corpus callosum. This procedure is used especially in case of atonic seizures, with 70% of the patients treated surgically displaying seizure reduction.<sup>40</sup>

### Non-resection techniques

- *Gamma knife radiosurgery.* This technique consists of the destruction of a small volume of brain tissue by applying a high dose of radiation (gamma particles emitted by radioactive cobalt). This radiation is applied stereotactically in a single session and any radiation reaching surrounding areas is minimal. It is used in selected patients with mesial temporal epilepsy, hypothalamic hamartoma-related epilepsy, and cavernoma-related epilepsy.

- *Deep brain stimulation.* Deep brain stimulation is based on the potentially regulating role played by subcortical structures in ES genesis and transmission. Stimulation has been targeted at the cerebellum, thalamic and subthalamic nuclei, caudate nucleus, hypothalamic nucleus, and substantia nigra. The SANTE study, which used bilateral stimulation of the anterior nuclei of the thalamus, showed a 56% median reduction in seizure frequency, and 54% of patients had a seizure reduction of at least 50%<sup>41</sup> (LE II).
- *Vagus nerve stimulation.* This procedure consists of periodical stimulation of the vagus nerve by placing helical bipolar stimulating leads around the cervical portion of the neck. A wire connects the leads to a pulse generator located on the thoracic wall. The technique reduces ES frequency in patients with drug-resistant epilepsy who are not candidates for resection surgery.<sup>42–44</sup> A recently published meta-analysis reviewing the published studies with a level of evidence of I, II, and III, and including a total of 3321 patients, showed a median ES reduction of 44.6% after a mean follow-up period of 10 months. Seizure frequency decreased significantly by the first year of follow-up after surgery (51% if >1 year,  $P < .001$ ). Of the patient total, 50.6% experienced an ES reduction of >20% (Engel classes I-III), with 4.6% of patients becoming seizure-free<sup>45</sup> (LE I). In patients younger than 6 years, ES

reduction was even higher (62.0%). ES reduction reached 47.8% in 93 patients with Lennox–Gastaut syndrome.<sup>45</sup> It has also been proved effective and well-tolerated in patients with other epileptic encephalopathies, such as Dravet syndrome, and epilepsy with myoclonic-astatic seizures<sup>46</sup> (LE IV). Vagus nerve stimulation is now used for more epilepsy types than focal epilepsy, its initial indication. It has also been used in idiopathic generalised epilepsy, patients with repeated episodes of status epilepticus, and in elderly patients<sup>47–49</sup> (LE IV).

- **Trigeminal nerve stimulation.** This technique has been recently approved for use in the European Union as adjunctive treatment for drug-resistant epilepsy in adults and children older than 9 years. In a randomised controlled trial, 40.5% of the patients responded to treatment after a follow-up period of 18 weeks.<sup>50</sup>

Fig. 2 lists the therapeutic actions after a first ES as recommended by consensus of the authors of the guidelines on surgery for epilepsy.

## Other non-surgical procedures

### Ketogenic diet

The ketogenic diet aims to replace carbohydrates with lipids. Metabolism of fatty acids generate ketone bodies (KB) (beta-hydroxybutyric acid, acetoacetic acid, and acetone to a lesser extent), which become the source of energy for the brain. Ketogenic diet promotes synthesis of glutamine (precursor of gamma-aminobutyric acid, an inhibitory neurotransmitter), which is structurally similar to GABA and would therefore have a direct antiepileptic effect. This treatment can be beneficial for children,<sup>51,52</sup> and it is the treatment of choice in cases of pyruvate dehydrogenase complex deficiency and lack of glucose transporter (GLUT-1). The treatment should be started at an early stage to allow the brain to use KB as an energy source<sup>53</sup> (LE III). In Lennox–Gastaut syndrome, ketogenic diet will be especially effective for reducing myoclonic and atonic seizure, and results in seizure freedom in up to 16% of these patients<sup>54</sup> (LE III). Current data suggest that this diet may have a similar effect in adults and in children.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### References

1. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51:1069–77.
2. Shorvon SD, Goodridge DMG. Longitudinal cohort studies of the prognosis of epilepsy: contribution of the National General Practice Study of Epilepsy and other studies. *Brain*. 2013;136:3497–510.
3. Ramos-Lizana J, Aguilera-López P, Aguirre-Rodríguez J, Cassinello-García E. Response to sequential treatment schedules in childhood epilepsy: risk for development of refractory epilepsy. *Seizure*. 2009;18:620–4.
4. Sillanpää M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. *Brain*. 2009;132:989–98.
5. Picot MC, Baldy-Moulinier M, Daurès JP, Dujols P, Crespel A. The prevalence of epilepsy and pharmaco-resistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia*. 2008;49:1230–8.
6. Gilioli I, Vignoli A, Visani E, Casazza M, Canafoglia L, Chiesa V, et al. Focal epilepsies in adult patients attending two epilepsy centers: classification of drug-resistance, assessment of risk factors, and usefulness of new antiepileptic drugs. *Epilepsia*. 2012;53:733–40.
7. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919–26.
8. Sazgar M, Bourgeois BF. Aggravation of epilepsy by antiepileptic drugs. *Pediatr Neurol*. 2005;33:227–34.
9. Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. *Epilepsia*. 2009;50:501–9.
10. French JA, Faught E. Rational polytherapy. *Epilepsia*. 2009;50 Suppl. 8:63–8.
11. Rowan AJ, Meijer JW, de Beer-Pawlikowski N, van der Geest P, Meinardi H. Valproate-ethosuximide combination therapy for refractory absence seizures. *Arch Neurol*. 1983;40:797–802.
12. Pisani F, Oteri G, Russo MF, di Perri R, Perucca E, Richens A. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia*. 1999;40:1141–6.
13. Villanueva V, López-Gomáriz E, López-Trigo J, Palau J, García M, Villarroya T, et al. Rational polytherapy with lacosamide in clinical practice: results of a Spanish cohort analysis RELACOVA. *Epilepsy Behav*. 2012;23:298–304.
14. Kwan P, Brodie MJ. Combination therapy in epilepsy. When and what to use? *Drugs*. 2006;66:1817–29.
15. Armijo JA, Herranz JL. Rational combination therapy in epilepsy. III. Possible associations between antiepileptic drugs. *Rev Neurol*. 2007;45:236–44.
16. Ben-Menachem E. Medical management of refractory epilepsy-practical treatment with novel antiepileptic drugs. *Epilepsia*. 2014;55:3–8.
17. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. *Epilepsia*. 2010;51:7–26.
18. Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. *J Neurol Neurosurg Psychiatry*. 2012;83:810–3.
19. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol*. 2007;62:375–81.
20. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. *Brain*. 2001;124:1683–700.
21. Binnie CD, Polkey CE. International League Against Epilepsy. Commission on Neurosurgery of the International League Against Epilepsy (ILAE) 1993–1997: recommended standards. *Epilepsia*. 2000;41:1346–9.
22. Pre-surgical evaluation for epilepsy surgery – European standards. European Federation of Neurological Societies Task Force. *Eur J Neurol*. 2000;7:119–22.
23. Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: Recommendations of

- the Subcommittee for Pediatric Epilepsy Surgery. *Epilepsia*. 2006;47:952–9.
24. Englot DJ, Chang EF. Rates and predictors of seizure freedom in respective epilepsy surgery: an update. *Neurosurg Rev*. 2014; <http://dx.doi.org/10.1007/s10143-014-0527-9>.
  25. Gumnit RJ, Walczak TS, National Association of Epilepsy Centers. Guidelines for essential services, personnel and facilities in specialized epilepsy centers in the United States. *Epilepsia*. 2001;42:804–14.
  26. Grupo de Cirugía Funcional de la Sociedad Española de Neurocirugía (SENEC). Guías clínicas para la cirugía de la epilepsia y de los trastornos del movimiento. *Neurocirugía (Astur)*. 2009;20:329–34.
  27. Guerrini R, Scerrati M, Rubboli G, Esposito V, Colicchio G, Cossu M, et al. Overview of presurgical assessment and surgical treatment of epilepsy from the Italian League Against Epilepsy. *Epilepsia*. 2013;54 Suppl. 7:35–48.
  28. Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology*. 2003;60:538–47.
  29. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal lobe epilepsy. *N Engl J Med*. 2001;345:311–8.
  30. Wyler AR, Hermann BP, Somes G. Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery*. 1995;37:982–90.
  31. Hermann B, Davies K, Foley K, Bell B. Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: a randomized prospective clinical trial. *Epilepsia*. 1999;40:1070–6.
  32. Engel J, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy. A randomized trial. *JAMA*. 2012;307:922–30.
  33. Choi H, Sell RL, Lenert L, Muennig P, Goodman RR, Gilliam FG, et al. Epilepsy surgery for pharmacoresistant temporal lobe epilepsy: a decision analysis. *JAMA*. 2008;300:2497–505.
  34. Devaux B, Chassoux F, Guenot M, Haegelen C, Bartolomei F, Rougier A, et al. Epilepsy surgery in France. *Neurochirurgie*. 2008;54:453–65.
  35. Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blümcke I, Carreño M, Gizewski ER, et al. Cavernoma-related epilepsy: review and recommendations for management – report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2013;54:2025–35.
  36. Cook SW, Nguyen ST, Hu B, Yudovin S, Shields WD, Vinters HV, et al. Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. *J Neurosurg*. 2004;100:125–41.
  37. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain*. 2005;128:1188–98.
  38. Bell ML, Rao S, So EL, Trenerry M, Kazemi N, Matt Stead S, et al. Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. *Epilepsia*. 2009;50:2053–60.
  39. Wetjen NM, Marsh WR, Meyer FB, Cascino GD, So E, Britton JW, et al. Intracranial electroencephalography seizure onset patterns and surgical outcomes in nonlesional extratemporal epilepsy. *J Neurosurg*. 2009;110:1147–52.
  40. Stigsdotter-Broman L, Olsson I, Flink R, Rydenhag B, Malmgren K. Long-term follow-up after callosotomy – a prospective, population based, observational study. *Epilepsia*. 2014;55:316–21.
  41. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51:899–908.
  42. Ben-Menachem E, Mañon-Espaillet R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. *Epilepsia*. 1994;35:616–26.
  43. Handforth A, deGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998;51:48–55.
  44. Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2013;81:1453–9.
  45. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg*. 2011;115:1248–55.
  46. Cersósimo RO, Bartuluchi M, de los Santos C, Bonvehi I, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in patients with epileptic encephalopathies. *Childs Nerv Syst*. 2011;27:787–92.
  47. Kostov H, Larsson PG, Roste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy? *Acta Neurol Scand*. 2007;115 Suppl. 187:55–8.
  48. Sierra-Marcos A, Maestro I, Rodríguez-Orsorio X, Miró J, Donaire A, Aparicio J, et al. Successful outcome of episodes of status epilepticus after vagus nerve stimulation: a multicenter study. *Eur J Neurol*. 2012;19:1219–23.
  49. Gallo BV. Epilepsy, surgery, and the elderly. *Epilepsy Res*. 2006;68 Suppl. 1:S83–6.
  50. DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology*. 2013;80:786–91.
  51. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary for epilepsy. *Cochrane Database Syst Rev*. 2012;3:CD001903.
  52. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008;7:500–6.
  53. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Bergqvist AGC, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50:304–17.
  54. Lemmon ME, Terao NN, Ng YT, Reisig W, Rubenstein JE, Kossoff EH. Efficacy of the ketogenic diet in Lennox–Gastaut syndrome: a retrospective review of one institution’ experience and summary of the literature. *Dev Med Child Neurol*. 2012;54:464–8.